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Regional Patterns in the Incidence of Aplastic Anemia in Thailand

Surapol Issaragrisil,[1]* Paul E. Leaverton,[2] Kanchana Chansung,[3] Tharatorn Thamprasit,[4] Yaowarat Porapakham,[5] Sathit Vannasaeng,[1] Anong Piankijagum,[1] David W. Kaufman,[6] Theresa E. Anderson,[6] Samuel Shapiro,[6] Neal S. Young,[7] and the Aplastic Anemia Study Group

[1]Department of Medicine, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand
[2]Department of Epidemiology and Biostatistics, College of Public Health, University of South Florida, Tampa, Florida, USA
[3]Department of Medicine, Faculty of Medicine, Khonkaen University, Khonkaen, Thailand
[4]Department of Medicine, Faculty of Medicine, Prince of Songkla University, Songkla, Thailand
[5]Asian Institute for Health Development, Mahidol University, Bangkok, Thailand
[6]Slone Epidemiology Unit, Boston University School of Medicine, Boston, Massachusetts, USA
[7]Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

The annual incidence of aplastic anemia has been determined in a rigorous and standardized epidemiologic study conducted in Thailand. A total of 374 cases were identified over a period of 3–6 years in three geographically defined and distinct regions of the country; Bangkok, Khonkaen in the northeast, and Songkla in the south. The incidence was 3.9 cases per million persons in Bangkok, 3.0 per million in Songkla, and 5.0 per million in Khonkaen. These rates are as high or higher than in any region of Europe or Israel as reported in the International Agranulocytosis and Aplastic Anemia Study, in which the methods and case definition were the same. Rates were stable over the course of the study. There were marked differences in incidence between northern and southern rural regions of Thailand, and among Bangkok suburbs. These differences, together with an unusual peak in the incidence among young people in Bangkok, suggest the possibility of occupational and environmental factors in the etiology of aplastic anemia. Am. J. Hematol. 61:164–168, 1999. © 1999 Wiley-Liss, Inc.

Key words: aplastic anemia; incidence; epidemiology; Thailand

INTRODUCTION

Aplastic anemia is a rare but severe disease of uncertain etiology [1]. The incidence appears to vary geographically. A long-standing impression of practicing hematologists in the Orient, and their visitors from the West, has been that aplastic anemia is relatively more common in Asian hematologic clinics [2–4]. Imprecise prevalence figures, derived from population surveys and hospital admission data, have suggested rates as much as 10-fold higher in China, Japan, and Korea than in Europe and the United States [5–7]. Based on an earlier 1-year incidence study conducted in Bangkok in 1989, we documented an incidence for this city of 3.7 per million [8]. Though not as high as anticipated from historical anecdotal reports, that rate is almost twice that of the average incidence reported from several regions in Europe and Israel in the International Agranulocytosis and Aplastic

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The Aplastic Anemia Study Group: S. Sompradeekul, T. Vuttivatanakul, C. Sriratanasatavorn, C. Yamcharoen, P. Laewsiri, S. Kittimongcolporn, K. Tepmongkol, R. Wongkongdej, R. Vejjapinand, V. Kiatvirakul, K. Karang, S. Jiraprayuklert, Y. Jiratanyasakul, T. Intragumthornchai, S. Chancharunee, V. Suvatte, P. Supradij, V. Chinarat, S. Laohavinij, V. Prayoonwiwat, S. Angkuravorakul, V. Atichartkarn, A. Chuansamrit, S. Chutipong, P. Hathirat, P. Isarangkura, A. Jetsrisuparb, S. Jootar, N. Kiatkachorntada, V. Laosombat, A. Lekhakul, V. Makornkaewkayoon, P. Nitiyanant, P. Seksan, J. Sirijirachai, D. Sonakul, T. Srichaikul, T. Sripaisal, P. Sucharitchan, S. Sukpanichnand, S.Y. Sukpanichnand, N. Suwanwela, C. Tantechanurak, K. Tanyavudh, S. Visudhiphan, W. Wanachiwanawin, P. Watananukul.

*Correspondence to: Surapol Issaragrisil, M.D., Division of Hematology, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. E-mail: sisis@mahidol.ac.th

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Anemia Study (IAAAS), and it was higher than the maximum rate (3) seen in any of those regions [9].

Our earlier report [8] was based on a total of 32 cases in Bangkok seen in 1989. During the 6-year period 1989–1994, a total of 207 cases were identified in that region. Two rural areas in Thailand, Khonkaen, and Songkla were also included in the study during the last 38 months of this time period; 167 cases were identified in those two regions. Thus, it was possible to compare rural and urban rates in Thailand. The large number of cases ascertained in a standardized manner in carefully defined geographic regions provide, for the first time, accurate estimates of aplastic anemia incidence in three distinct areas of an Asian country. In addition, because the methods and case definition were the same as those used in the IAAAS, international comparisons can be made.

MATERIALS AND METHODS

Identification and Ascertainment of Cases

Forty major hospitals, comprising all acute-care institutions with at least 100 beds in greater Bangkok (including Bangkok and its suburbs) participated in the Bangkok part of the study. In Khonkaen, there were eight hospitals and in Songkla, there were seven. In all three study regions, cases with aplastic anemia are treated in large hospitals by hematologists; in small hospitals, suspected cases are known to the physicians in charge. Potential cases were identified by study personnel, who contacted either hematologists or physicians in charge as appropriate, by personal visit or by telephone, at least every other week. Eligible patients were required to meet at least two of the following three peripheral blood count criteria; white-blood-cell count $\leq 3.5 \times 10^9$/l, platelet $\leq 50 \times 10^9$/l, and either hemoglobin concentration ≤ 100 g/l, or hematocrit $\leq 30\%$ with a reticulocyte count $\leq 30 \times 10^9$/l. Patients who had received chemotherapy, immunotherapy, or radiotherapy were excluded. In Thailand, the bone marrow aspirates of all cases of pancytopenia are examined as a matter of routine medical practice; a biopsy is always obtained if the aspirate specimen is hypocellular. To exclude alternative diagnoses, the final acceptance of cases for inclusion in the study required a characteristic hypocellular bone marrow biopsy without gross marrow fibrosis, and absence of infiltration by leukemic, lymphomatous, or cancer cells. These criteria are identical to those used in the IAAAS [9]. Final diagnoses of aplastic anemia were verified by two hematologists (S.I. and A.P.). All patients first diagnosed from 1 January 1989 through 31 December 1994, who resided in greater Bangkok were included, and for Khonkaen and Songkla, cases diagnosed from 1 November 1991 through 31 December 1994 were included.

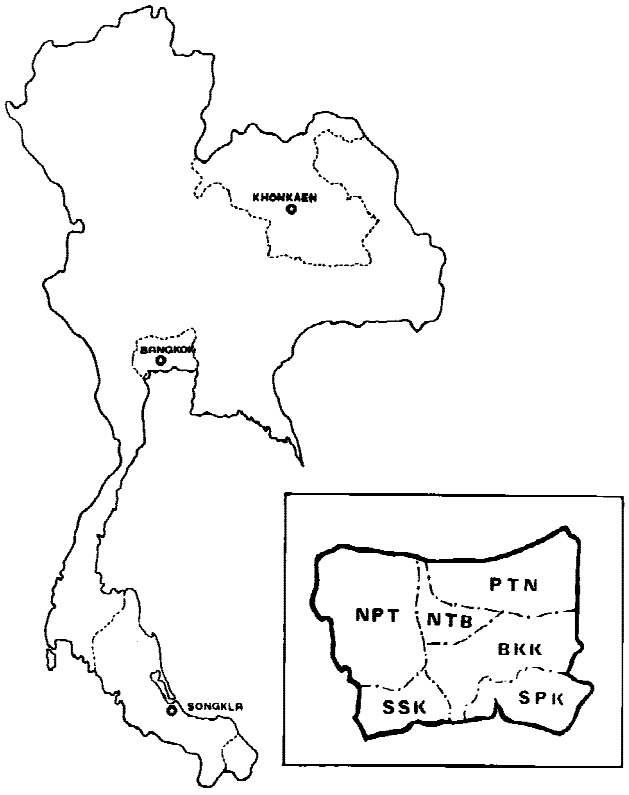

Fig. 1. Map of Thailand and study regions.

Geographic Regions and Population Denominators

Greater Bangkok included the metropolitan area plus the suburbs of Nonthaburi, Nakornpathom, Pathumthani, Samutprakarn, and Samutsakorn. The Khonkaen region in the northeast included the provinces of Khonkaen, Kalasin, Mahasarakam, Loei, Nongkai, Udonthani, and Royed. The Songkla region in the south included Songkla, Yala, Pattani, Satoon, Nakornsrithammarat, and Trang provinces. The study regions are shown on the maps in Figure 1.

Population data for the period from 1989 to 1994 were provided by the Central Registration Office of the Ministry of the Interior, as projected from census data collected in 1991. For the Bangkok region, the total was approximately 8,754,000; for Khonkaen, it was 7,644,000; and for Songkla, it was 4,994,000. We also utilized projections from the census data to estimate the population age and sex distributions in all participating regions.

RESULTS

The annual incidence of aplastic anemia in three regions is shown in Table I. In Bangkok (207 cases), the overall incidence over the 6-year period, 1989–1994, was 3.9 per million per year. The incidence in Khonkaen (119

TABLE I. Annual Incidence of Aplastic Anemia According to Region

Region	Population	No. of cases	Annual rate per million
Bangkok (2/89–12/94)	8,754,000	207	3.9
Khonkaen (11/91–12/94)	7,644,000	119	5.0
Songkla (11/91–12/94)	4,994,000	48	3.0

cases) was higher, at 5.0 per million, and in Songkla (48 cases) it was lower, at 3.0 per million. These three rates differed statistically ($X^2 = 10.81$, $P < 0.01$).

As shown in Table II, there was considerable variation in the incidence among the various suburbs of Bangkok. In the contiguous north and northwest suburbs of Nakornpathom and Pathumthani, the rates were relatively low—2.5 and 2.4 per million. In metropolitan Bangkok, the rate was intermediate, at 3.6 per million. In the nearby northwest suburb of Nonthaburi and in the contiguous southeastern and southern suburbs of Samutprakarn and Samutsakorn, the rates were relatively high—5.7, 6.2, and 6.1 per million. With the exception of Pathumtani, all of the individual rates had stable numerators of at least 10 cases. Again, these rates were of statistically significant difference ($X^2 = 21.11$, $P < 0.01$). Table III displays the incidence in Bangkok according to age and sex. Again, there were at least 10 cases in each category. Among both males and females there was a clear double peak in the 15–24-year-old age group, with rates of 7.6 and 6.0 per million, respectively, and in those aged at least 60 years, with rates of 9.3 and 6.3 per million. Overall, the incidence was somewhat higher among males, at 4.2 per million, compared to 3.7 per million among females. The different incidence rates by age group were statistically significant ($X^2 = 49.95$, $P < 0.01$).

With fewer cases from Khonkaen and Songkla, only overall age and sex-specific rates are given. As shown in Table IV, there was a steady increase in the incidence by age in both regions, unlike the double peak pattern observed in Bangkok. In the oldest age group (≥60 years), the incidence was 15 per million in Khonkaen, and 25 per million in Songkla. The patterns according to sex, shown in Table V, were somewhat different. As in Bangkok, the disease was somewhat more common among males in Khonkaen (5.2 vs. 4.7 per million among females). In Songkla, by contrast, the incidence was higher among females (3.4 vs. 2.7 per million among males).

DISCUSSION

Accurate determination of the incidence of aplastic anemia in a geographically defined population requires both active case ascertainment to identify all new cases over a specified time period, and accurate diagnosis, based on a standardized definition, complete blood counts and the correct interpretation of bone marrow pathology [10]. Because the disease is so rare, it is also necessary to monitor a very large base population to identify enough cases for stable estimates to be made. For these reasons, few such investigations have been performed or published. We believe that rigorous standards for completeness and accuracy were substantially achieved in the present study, which is the largest conducted to date. The cooperation of hematologists and physicians was obtained in all relevant hospitals in the three study regions, and cases were actively identified by study personnel. The peripheral blood values that were the basis for initial case identification were sufficiently stringent that patients who met them would nearly always have displayed symptoms requiring medical attention. We judge it unlikely that many eligible cases escaped coming to notice during the study period.

As previously reported [8] the incidence in Bangkok is just under four new cases of aplastic anemia per million persons per year, or about twice the rate determined in systematic studies performed in Western countries based on the same methods. The present estimate is based upon 6 consecutive years of surveillance, and with a total of 207 cases, it is highly stable. The IAAAS, conducted in Europe and Israel in the 1980s, obtained an overall annual incidence rate of 2 per million [9]; this was confirmed in a separate, similarly conducted study in France [11], and is also consistent with other less formal surveys recently conducted in England and Denmark [12–14]. Though some older studies reported apparently higher rates of aplastic anemia in the West [15–18], they are flawed by less stringent diagnostic criteria and by the use of retrospective designs to identify cases that included voluntary reporting and review of medical records or death certificates.

After the present study began, it was extended to two rural areas of Thailand. The incidence of aplastic anemia in Khonkaen, an agricultural region in the northeast, was some 25% higher than in Bangkok, possibly due to pesticides or other agricultural exposures [19]. It is interesting that in the other rural region—Songkla in the south—the incidence was about 25% lower than in Bangkok and 40% lower than in Khonkaen. Both of the rural rates were also stable, with numerators of 119 and 48 cases, respectively. With regard to other countries in Southeast Asia, preliminary results suggest that aplastic anemia may also be relatively common: about five per million in Sabah province in Malaysia [20] and, for males, about 7 per million in Ho Chi Minh City in Vietnam [21]. A very large incidence survey performed in China produced a rate of 7.4 per million over an area encompassing 21 provinces, municipalities, and regions [22]; however, no information on the design and execution of the study was provided. Given both the methodologic questions and the

TABLE II. Annual Incidence of Aplastic Anemia in Bangkok and Suburbs

Locality	1991 Population (thousands)	Cases (6-year total)	Annual incidence per million (1989–1994)
Metropolitan Bangkok	5,993	130	3.6
Nonthaburi	507	20	5.7
Nakornpathom	642	10	2.5
Pathumthani	419	6	2.4
Samutprakarn	705	29	6.2
Samutsakorn	327	12	6.1
Total Greater Bangkok (metropolitan + suburbs)	8,754	207	3.9

TABLE III. Annual Incidence of Aplastic Anemia in Greater Bangkok, 1989–1994 According to Age and Sex

	Annual rate per million (no. of cases)		
Age group	Male	Female	Total
0–14	2.0 (16)	2.2 (16)	2.1 (32)
15–24	7.6 (38)	6.0 (30)	6.8 (68)
25–39	4.1 (32)	1.8 (14)	2.9 (46)
40–59	2.9 (12)	6.2 (26)	4.6 (38)
≥60	9.3 (12)	6.3 (10)	7.7 (22)
Total	4.2 (110)	3.7 (97)	3.9 (2.7)

TABLE IV. Annual Incidence of Aplastic Anemia in Khonkaen and Songkla 11/91–12/94 According to Age

	Annual rate per million (no. of cases)	
Age group	Khonkaen	Songkla
0–14	0.4 (3)	0.5 (3)
15–24	3.5 (20)	1.8 (6)
25–39	6.6 (34)	1.2 (4)
40–59	11 (42)	4.9 (11)
≥60	15 (20)	25 (24)
Total	5.0 (119)	3.0 (48)

TABLE V. Annual Incidence of Aplastic Anemia in Khonkaen and Songkla, 11/91–12/94 According to Sex

Region	Males	Females
Khonkaen		
Population (thousands)	3,850	3,794
Cases	63	56
Annual incidence (per million)	5.2	4.7
Songkla		
Population (thousands)	2,504	2,490
Cases	21	27
Annual incidence (per million)	2.7	3.4

rarity of the disease, formal statistical comparisons with the present results are not appropriate. Nevertheless, the high rates reported from the other investigations are consistent and suggest that the incidence of aplastic anemia in several Asian countries is likely to be greater than in Europe. Earlier estimates that were even higher can now be viewed as misleading and inflated, mainly because they were based on the very large numbers of patients seen at central referral hospitals with huge catchment areas, such as Siriraj Hospital in Bangkok and the National Hematology Institute in Tianjin, China.

The geographic differences among the three regions of Thailand may relate to different distributions of risk factors identified in the case-control component of this study, which include poverty [23], farming [19], and high rates of enteric virus infection [24]. Environmental and occupational patterns differ between northern and southern Thailand, and some or all of these risk factors may contribute to the higher incidence rate observed in Khonkaen. Already ruled out are drugs [25] and household pesticides [26], which are commonly used with few restrictions in Thailand, but contribute minimally, if at all, to the risk of aplastic anemia. Under active investigation in the ongoing study are the role of different practices of rice cultivation, exposure to water contaminated by human and animal feces, and herbicide and pesticide use in agriculture; laboratory efforts are directed to known or novel viruses as inciting agents in bone marrow failure.

A 2.5-fold difference in disease rates within different regions of the greater Bangkok area was also noted, and it persisted throughout the 6 years of study. The highest incidence was observed in Samutprakarn, Samutsakorn, and Nonthaburi, areas containing a greater number of chemical industries and industries incidentally utilizing chemicals. However, Bangkok is not easily divisible into industrial and residential zones, and small scale factories are scattered throughout the region. In China, benzene has been the focus of study, and surveys of exposed factory workers have reported apparently high rates of aplastic anemia and hematopoietic malignancies in this population [27]. In our experience to date, solvent exposure has appeared as at most a minor contributor to the etiology of aplastic anemia. In the IAAAS, marked differences in the rates of aplastic anemia were also observed among different metropolitan areas, without clear explanation (from a low of 0.6 in Budapest to high values of 3.0 in Milan and 2.4 in Ulm) [9].

The age distribution of the Bangkok cases differs markedly from the steady increase in the incidence with

increasing age seen in rural Thailand and most other countries. In Bangkok, there was not only the usual increase among the elderly but another peak in older children and young adults of both sexes. The rate in the 15–24-year-old group, 6.8 per million, is almost 4 times higher than that seen in the same age group in the IAAAS [9]; that also suggests the possibility of unique environmental or occupational exposures, although a specific hypothesis as to what these may be has not been developed. A similar peak in younger patients was observed for patients with aplastic anemia admitted for treatment to major American referral hospitals [28]. In summary, by using accepted and rigorous methodology, we have measured high rates of aplastic anemia in both urban and rural regions of Thailand. Regional and age-specific differences in the incidence rates now accurately quantified for Thailand. These results are compatible with preliminary results reported from other Asian countries, and are more consistent with environmental than genetic factors in the causation of aplastic anemia. Identification of these factors—biological pathogens or chemical toxins—should come from the combination of population-based and laboratory scientific approaches.

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